EXPERIMENTAL HUMAN EXPOSURE TO PROPYLENE GLYCOL DINITRATE

Final Report

By

Sep 73

N00014-71-A-0424-0001

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This investigation was supported by contract from the Bureau of Medicine and Surgery, Department of the Navy.

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PREPARED FOR
BUREAU OF MEDICINE AND SURGERY

SEPTEMBER 1973

SYNOPSIS - ABSTRACT

Human volunteers were exposed to PGDN vapor at concentrations of 0.03, 0.1, 0.2, 0.35, 0.5, and 1.5 ppm. Exposure to concentrations of 0.2 and greater produced disruption of the organization of the visual evoked response (VER) and headache in the majority of subjects. Subjects repeatedly exposed to 0.2 ppm for 8 hours on a daily basis developed a tolerance to headache induction, but the alteration in VER morphology appeared cumulative. Marked impairment in balance became manifest after exposure to 0.5 ppm for $6\frac{1}{2}$ hours while 40 minutes of exposure to 1.5 ppm added eye irritation to the list of symptoms.

1,2-Propylene glycol dinitrate (PGDN), a red-orange liquid with a disagreeable odor, is the major volatile constituent of Otto Fuel, a torpedo propellent now being introduced into the U. S. Naval fleet. The fuel is named for its inventor, Otto Reitlinger, who died in 1970. Accidental over-exposure to PGDN, a potential methemoglobin former, has resulted in a spectrum of illnesses ranging from headache, nasal congestion, dizziness, and eye irritation to vasomotor collapse and unconsciousness.

The industrial Threshold Limit Value (TLV) for PGDN is 0.2 ppm. This standard is based on the human experience in ammunition plants where PGDN breathing zone concentrations were carefully related to the absence of untoward symptoms. The industrial TLV standard has been adopted by the U. S. Navy, but concern over the paucity of data regarding the effects of PGDN on human performance and physiology prompted this investigation.

EXPERIMENTAL PROCEDURE

Twenty human volunteers were exposed to a range of PGDN vapor concentrations designed to yield information regarding human response to acute over-exposure and to repeated daily exposures to the current TLV. The investigation was performed with strict adherence to the ethical and technical requirements for human inhalation experimentation previously detailed[1]. Informed consent was obtained after the nature of the procedures had been fully explained to the volunteer subjects.

Subjects. Seventeen healthy male college students ranging in age from 22 to 25 years served as paid volunteers for the exposure studies. Additional clinical observations were made on three members of the research staff during times of their exposure: two males, ages 45 and 51; and a female, age 24. None of the subjects were smokers and none was taking medication. Prior to exposure each was given a comprehensive medical examination which included a complete history and physical examination and the laboratory studies listed below.

Exposure Schedule. Table I lists the number of subjects and the PGDN vapor concentrations to which they were exposed for each of the experiments. Eight subjects participated in experiments 1 - 16, while a second group of nine subjects participated in the remainder of the experiments. Each group underwent a training program in the chamber (experiments 1 - 12, 17 - 27, 32 - 35, and 38 - 39). The experiments were conducted in a double-blind mode, however, in those experiments in which the odor of PGDN was detectable both the subjects and the research staff were aware that exposure to PGDN was occurring although the magnitude of the exposure was not disclosed to them.

Exposure Chamber. The experiments were conducted in the controlled-environment chamber which was a room measuring 20 x 13 x 8 feet high. The chamber contained a $3\frac{1}{2}$ x 4 x $6\frac{1}{2}$ feet audiometric booth and a 3 x 6 x 8 feet laboratory facility. The air flow through the chamber compartments to the exhaust was 500 cubic feet/minute, which created a slight negative pressure

within the exposure complex. The ambient temperature within the chamber was maintained at 72 - 74° F., while the relative humidity ranged between 45 - 55%. The PGDN was introduced into the chamber's atmosphere by blowing air at a rate of 10 - 15 liters/min across a pyrex reservoir of the compound situated in the inlet air supply duct. Eighty per cent of the contaminated air was recirculated through the environmental chamber.

Material Used. The PGDN used in these experiments was vaporized from a sample of Otto Fuel which had been in storage for 18 months. The fuel contained a non-volatile stabilizer and a desensitizer.

Analysis of Exposure Chamber Atmosphere. The concentration of PGDN in the chamber atmosphere was recorded continuously by an infrared spectrophotometer equipped with a 20-meter path-length gas cell which was continuously flushed with air drawn from the chamber through $\frac{1}{4}$ inch diameter polyethylene tubing. The absorbance at 12.0 μ was measured. A gas chromatograph equipped with an electron capture detector and an automatic, sequential sampling valve provided the second, independent analytical method.

Clinical Testing. Prior to each exposure a repeat physical examination was performed on each subject. At this time each was given a subjective symptom check list to complete. This included questions regarding the presence of headache, eye or throat irritation, nausea, chest pain, abdominal pain, and chemical odor. This check list was then taken by the subject into the

chamber and each hour this symptom review was repeated. Prior to and following the exposures the following laboratory determinations were made: complete blood count, blood nitrate [2], carboxyhemoglobin saturation, methemoglobin [3], SGOT, SGPT, BUN, alkaline phosphatase, bilirubin, serum electrolytes, creatinine, blood PGDN, alveolar breath PGDN, urinalysis, and nitrate and nitrite urinary excretion. The following studies completed the pre-exposure evaluation: spontaneous EEG, visual evoked response [4], and EKG lead II rhythm strip by telemetry.

After entering the environmental chamber the subjects were under continual visual surveillance by medical personnel and all important chamber activities were video taped by closed circuit TV. First, each subject performed a Romberg test followed by a heel-to-toe test with his eyes open, then with his eyes closed. The subjective symptom check list procedure was begun. Then, every hour the blood pressure and a lead II EKG rhythm strip obtained. The following additional clinical studies were performed on the subjects who were exposed for single 4- and 8-hour periods during the final hour of their exposure: computerized spirometry measurement which included the maximum mid-expiratory flow rate, spontaneous EEG, visual evoked response, visual acuity measurement, audiometric measurement, exercise EKG, Marquette time estimation test [5], 10- and 30-second time estimation tests [6], Crawford collar-and-pin coordination test, and the Flanagan arithmetic, coordination, and inspection tests. During each of the 8-hour exposures the

mechanical performance of the heart of one seated subject was monitored for the first 4 hours using impedance cardiography[7].

Five minutes prior to exiting from the exposure chamber each subject repeated the modified Romberg test and performed the heel-to-toe test. Then a venous blood sample for PGDN determination was obtained by having the subject stick his arm through an arm-port in the chamber wall into the uncontaminated, adjacent laboratory. During the five successive exposures to PGDN 0.2 ppm for 8 hours, the same procedures were followed except that the testing previously begun during the final hour of exposure was commenced after five $\frac{1}{2}$-hours of exposure to accommodate the larger number of subjects.

Post-Exposure Surveillance: All subjects were placed under close medical surveillance for a 16-hour period following each exposure. Subjective responses were recorded 1, 2, 3, and 16 hours post-exposure. Alveolar breath samples for PGDN analysis were collected 5, 15, 30, 60 and 120 minutes post-exposure. A 24-hour urine specimen was collected and analyzed for total nitrate and creatinine. Fifteen minutes post-exposure a venous blood sample was obtained for the following analyses: PGDN, methemoglobin, nitrate, and CBC. Sixteen hours following each exposure the pre-exposure baseline studies were repeated.

Analysis of Breath and Blood for PGDN. Propylene glycol dinitrate was analyzed in human breath and blood using a gas chromatograph equipped with an electron capture detector[8]. Five to 50 microliter breath aliquots

were injected directly into a 1' x 18" Teflon column containing 3% SE-30 on Chromosorb W, 60/80 mesh operating at 75°C. The injector temperature was 170°C, while the detector temperature was 150°C. Five-milliliters aliquots of venous blood were extracted with n-hexane. One-microliter of the extract was injected into the gas chromatograph. Samples were compared to PGDN standards made up in hexane solution and PGDN air standards prepared in saran bags.

Data Analysis. Group F and t-tests were performed to compare baseline and control performance to performance data collected during exposure. Then paired t-tests were used to search for individual responses to PGDN exposure.

RESULTS

During the training sessions each subject evidenced the expected improvement in his ability to perform the Crawford collar-and-pin test, and the Flanagan coordination, inspection, and arithmetic tests. With the exception of the Crawford collar-and-pin test and the Flanagan inspection test, learning appeared complete for all of the tests administered before the first chamber exposure occurred.

PGDN: 0.03 ppm. The subjects were unable to detect the odor of the compound in the chamber atmosphere. One subject developed a mild frontal headache one hour into the exposure, but this cleared spontaneously within one

odor. No other untoward subjective symptoms or objective signs of illness were noted during or in the 24-hour period following the exposure. No decrement in test performance or alteration in monitored physiological parameters occurred (see PGDN Report, July 7, 1972 for performance data). All of the clinical chemistries remained within the limits of normal.

PGDN: 0.1 ppm. The subjects were unable to detect the odor of the compound in the chamber atmosphere. Two of the subjects did develop headaches during the course of the exposure. The same subject who had developed headache at the lowest concentration studied, developed a mild frontal headache occurring after three hours of exposure. The pain persisted for 90 minutes before spontaneously resolving. A second subject developed a frontal headache occurring after six hours of exposure and his pain persisted for several hours into the post-exposure period. The latter subject was given black coffee to drink immediately following exposure. The coffee seemed to ameliorate, but not completely alleviate the pain.

No other untoward subjective symptoms or objective signs of illness were noted during or in the 24-hour period following the exposure. No decrement in test performance or alteration in monitored physiological parameters occurred (see PGDN Report, July 7, 1972 for performance data). There were no changes in the clinical chemistries during or following the exposure.

PGDN: Single Exposures to 0.2 ppm. The nine subjects were exposed to PGDN 0.2 ppm on two occasions (experiments 31 and 40). During the first exposure, four of the nine subjects reported the odor to be mild in intensity. Within five minutes of exposure, they could no longer detect the odor. During their second exposure, three of these four reported they could detect the odor and again they were unable to smell it after five minutes of exposure.

During the first exposure to PGDN 0.2 ppm, none of the subjects exposed for one hour developed headache, while two of the three subjects exposed for four hours developed mild throbbing headaches after one and two hours of exposure. The first subject's headache persisted for one hour and resolved within minutes following exposure. The second subject's headache persisted for two hours into the post-exposure period before spontaneously resolving. All three of the subjects exposed for eight hours developed headaches after three to four hours of exposure. In one instance, the headache was mild and spontaneously resolved after one hour while the subject was still being exposed. The second subject developed a dull, bitemporal headache which became throbbing when he lay down. The headache persisted one hour into the post-exposure period, at which time he took two 5-grain aspirin tablets with one cup of coffee and noted complete subsidence of pain within three minutes. The third subject exposed for 8 hours developed a throbbing headache 3 hours into the exposure. The pain became progressively worse, reaching its maximum intensity one hour post-exposure, at which time the subject drank two cups of black coffee with some amelioration of pain. Three

and one-half hours post-exposure, the headache was still present and at this time the subject took two 5-grain aspirin tablets with two cups of coffee and went to bed. The headache was gone the next morning. This latter subject also complained of developing nasal congestion one hour into the run and definite eye irritation six hours into the run. Both the nasal congestion and eye irritation were present three and one-half hours post-exposure.

During the second exposure to PGDN 0.2 ppm, all of the subjects were exposed for eight hours, during which eight of the nine subjects developed headaches. These developed after two to five hours of exposure and initially were mild frontal or bitemporal headaches which tended to become more intense as the exposure continued. Four of these headaches resolved spontaneously within 15 minutes following cessation of exposure. The remainder of the headaches persisted from 1 to 3 hours into the post-exposure period before resolving without treatment. The subject who had had the most severe headache during the first 8-hour exposure to this concentration of PGDN, this time developed a mild headache after four hours which resolved within 15 minutes following exposure. This time the subject did not experience nasal congestion or eye irritation.

No other untoward subjective symptoms or objective signs of illness were noted during or in the 24-hour period following these two exposures. With the exception of the visual evoked response, which will be discussed in detail later, no decrement in test performance or alteration in monitored

physiological parameters occurred (Table II, Figures 1 - 21). There were no changes in the clinical chemistries during or following these exposures.

Repeated Daily Exposure to PGDN 0.2 ppm. The response of the subjects to their first 8-hour exposures to PGDN vapor 0.2 ppm is presented above. During the second consecutive day of exposure to PGDN 0.2 ppm none of the nine was able to detect the odor, but three subjects did develop headache after three hours of exposure. The headaches were mild in pain intensity and two of them resolved spontaneously 2 and 4 hours after onset while the subjects were still being exposed. The third subject's headache resolved within 15 minutes following cessation of exposure.

On the third consecutive day of exposure, three of the subjects were able to detect the odor of the compound upon entering the chamber. Within five minutes they could not detect this odor. On this third day, three subjects developed mild headache after 1, 3, and 5 hours of exposure. The subject who developed the first headache reported that it resolved spontaneously after one hour during the exposure. The other two headaches persisted 1 and 3 hours into the post-exposure period.

On the fourth day of exposure one subject reported that he was able to detect the odor of the compound during the first five minutes of the exposure. None of the subjects developed headache.

On the fifth successive day of exposure, three of the subjects reported they were able to detect the odor of the compound during the first five minutes

of exposure. One subject, the individual who had had the most severe headache during the first two days of exposure, developed a mild headache during the seventh hour of exposure which persisted for one hour before resolving spontaneously.

No other untoward subjective symptom or objective signs of illness were noted during or in the 16-hour periods following each of the five exposures. With the exception of the visual evoked response, no decrement in test performance or alterations in the monitored physiological parameters occurred. There were no changes in the clinical chemistries during or following these exposures.

PGDN: 0.35 ppm. Four of the nine subjects were able to detect the odor of the compound which was described as "mild". None was able to detect the odor after 5 minutes of the exposure.

Only the subjects exposed for 2 or 8 hours developed headache. Those exposed for 2 hours reported the presence of the headache shortly before exiting from the chamber. In one instance the headache cleared within five minutes after exposure. The second subject's headache cleared spontaneously two hours post-exposure, while the third headache was still present two hours post-exposure at which time the subject drank black coffee and noted complete clearing of the headache within one hour.

The subjects exposed for 8 hours reported the presence of headache after 3, 4, or 5 hours of exposure. One of these headaches cleared within 15

minutes following cessation of exposure. The other two headaches were reported to be very severe although one of these cleared spontaneously two hours following exposure. Because of the severity of the headache of the third of these subjects, 100% oxygen was administered via a face mask for 20 minutes. This greatly ameliorated the pain but it returned two hours post-exposure and persisted for an additional two hours.

One of the 2-hour subjects reported slight eye irritation beginning after 5 minutes of exposure and persisting throughout the exposure. The irritation subsided completely within 5 minutes after exposure.

No other untoward subjective symptoms or objective signs of illness were noted during or in the 24-hour period following the exposure. With the exception of the visual evoked response, no decrement in test performance or alteration in monitored physiological parameters occurred. All of the clinical chemistries remained within the limits of normal.

PGDN: 0.5 ppm. Four of the nine subjects reported they could detect a mild odor during the first 15 minutes of the exposure. Two of the subjects stated they could still smell the odor $1\frac{1}{2}$ hours into the exposure.

Seven of the nine subjects developed headache during the exposures. One of the subjects exposed for one hour developed a mild headache which resolved spontaneously without treatment one hour post-exposure. The three subjects exposed for 2 hours developed headache 20 minutes, 1 hour, and 1 3/4 hours into the run. Two of these subjects drank black coffee following

cessation of exposure and one reported that the coffee definitely ameliorated his pain. The other subject drank four cups of black coffee without relief. The third subject in this group refused coffee but took 10 grains of aspirin and reported relief of head pain within 60 minutes.

The subjects who were exposed for 8 hours developed headache after 2, 3, or 4 hours of exposure. These headaches were initially mild in intensity but became progressively worse and throbbing in nature. One of the subjects reported that he was dizzy and nauseated after 6 hours of exposure. All of the subjects reported that the headache was less painful within 5 minutes following cessation of exposure. All three consumed black coffee but only one noted definite amelioration of his pain.

Because of the severity of the headache in the three subjects being exposed for 8 hours, the modified Romberg test and heel-to-toe tests were performed after $6\frac{1}{4}$ hours after exposure and again after 8 hours of exposure immediately prior to exiting from the chamber. After $6\frac{1}{4}$ hours of exposure two of the subjects had abnormal heel-to-toe tests with their eyes closed. After 8 hours of exposure, all three subjects had abnormal modified Romberg tests as well as an abnormal heel-to-toe test performed with eyes closed. One subject was unable to perform a normal heel-to-toe test with his eyes open.

The three subjects with the abnormal neurological finding all showed a narrowing of their pulse pressure due to an elevation of their diastolic pressure. The mean elevation for the group was 12 mm Hg.

With the exception of the visual evoked response no other alteration in monitored physiological parameters or decrement in test performance occurred. All of the clinical chemistries remained within the limits of normal.

During this exposure, three members of the research staff, including one female, were exposed for $1\frac{1}{4}$ hours. All three developed a mild headache which lessened in severity following the consumption of black coffee.

PGDN: 1.5 ppm. All of the subjects were able to detect the odor of the compound upon entering the exposure chamber. Two subjects reported the odor to be mild, four reported it to be moderate, and two reported it to be strong in intensity. Within 20 minutes none of the subjects were able to detect the odor.

Three of the 8 subjects experienced slight eye irritation after 5 minutes of exposure. All of the subjects reported definite eye irritation after 40 minutes of exposure. This irritation persisted throughout the exposure period and resolved spontaneously within 5 - 8 minutes after cessation of exposure. During the time of eye irritation there was no evidence of conjunctivitis or excessive lacrimation.

All of the subjects developed headaches. Three subjects developed frontal headache after 30 minutes of exposure while the remaining subjects developed headache after 40 to 90 minutes of exposure. The headaches began as mild frontal headaches which became progressively severe and throbbing. So severe were the headaches that the exposure was terminated after 3 hours of exposure. At this time the pain was nearly incapacitating

was only the stoicism of the subjects, who had a high level of motivation, permitted an exposure of this duration. After exposure the subjects were given two cups of strong, black coffee. All reported that the coffee seemed to ameliorate the pain. Headaches did persist in the subjects for a period of time ranging from 1 to $7\frac{1}{2}$ hours into the post-exposure period.

PGDN Breath and Blood Concentrations. While the analytical method employed possessed sensitivity in the part per billion range, only trace amounts of PGDN were detected in the blood of the subjects during the higher exposures and in the expired breath in the immediate post-exposure period. During the exposure to PGDN 1.5 ppm, the amount of the compound extracted from the blood was less than 5 ppb, the limits of sensitivity of the method. The expired breath of the subjects during this exposure was 20 to 35 ppb after one hour of exposure. This concentration remained constant throughout the remainder of the exposure. Five minutes post-exposure only 1 - 4 ppb was detectable in the expired breath. None was present in the breath 15 minutes post-exposure.

Trace amounts of PGDN, 1 - 5 ppb, were detected in the 5-minute post-exposure breath samples of the subjects exposed to 0.35 and 5.0 ppm.

Blood Nitrate and Methemoglobin. This series of exposures was not of sufficient magnitude to elevate the blood nitrate or methemoglobin concentration above control values.

Visual Evoked Response. The peak-to-peak amplitude of the 3-4-5 wave complex, the most consistent characteristic of the VER from individual to

individual, as well as the latency of the peak of the 4-wave were used as objective measures to determine whether the VER had been altered as a result of exposure to PGDN. During the chamber experiments in which the subjects were not exposed to PGDN vapor, no significant alteration in the VER occurred. In figure 12 the responses from the three control runs in the second group of subjects are superimposed to illustrate the reproducibility of the VER response.

The first exposure to PGDN 0.2 ppm produced minimal alteration of the VER in the majority of subjects (figure 13). No consistent pattern of response was elicited. Exposure to a concentration of 0.35 ppm produced an increase in the peak-to-peak amplitude of the 3-4-5 complex in a number of subjects, particularly those exposed for 8 hours (subjects No. 37, 50, 67 in figure 14). The augmentation of the amplitude of the 3-4-5 complex was also produced as a result of exposure to 0.5 ppm (figure 15).

Exposure to PGDN 1.5 ppm produced dramatic alteration in the VER (figure 16). After 45 to 90 minutes of exposure, every subject exhibited an increased amplitude in the peak-to-peak voltage of the 3-4-5 complex of the VER which ranged from 10 to 70% above control levels. After 160 to 180 minutes of exposure, the subjects showed a strong tendency for the peak-to-peak voltage of the 3-4-5 complex to shift toward control levels. VER tracings obtained 48 hours after exposure from the subjects exposed for 3 hours suggest that it may take up to 24 hours following exposure of this magnitude for the VER to return to baseline levels.

Figures 17 through 21 presents the serial VER tracings obtained during the five consecutive days of exposure to PGDN 0.2 ppm. The response elicited from a given individual on any given day of the exposure sequence may be somewhat variable, however, there was an overall trend toward increased peak-to-peak amplitude of the 3-4-5 complex. The most striking feature of this sequence of exposure was the cumulative effect of serial exposure upon the VER. On each consecutive day, the control VER of each subject tended to have a higher peak-to-peak voltage than the control response of the previous day. This observation is highly suggestive of a cumulative effect of PGDN at this dose level.

Spontaneous Electrical Activity (EEG). The conditions of the experiment dictated that a limited array of cortical electrodes be utilized to record the spontaneous EEG. This array consisted of Pc and mid-frontal point midway between Fp1 and 2. These points were recorded against each other and against A_2 (left ear). EEG activity was recorded periodically during acquisition of the evoked visual response. The EEG records corresponding to the terminal periods of the VER stimulation sequence were utilized for comparison of control versus PGDN exposure. The standardized conditions for a VER recording provided good baseline conditions for EEG analysis during control and post-exposure samples. Under the conditions of these experiments, PGDN in the concentration range studied did not produce any consistent change in the spontaneous electrical activity of the cortex which could be detected by visual analysis of the tracings.

COMMENTS

Exposure of healthy males to PGDN vapor 0.2 ppm, the current TLV, produces headache and an alteration in the visual evoked response indicating that the compound is pharmacologically active at this dosage. Repetitive exposures to this concentration result in the development of tolerance to the compound so far as headache is concerned, but the disruption of the organization of the visual evoked response becomes increasingly more marked. Exposure to higher concentrations results in the more rapid onset of a more severe headache. At 0.5 ppm, marked disequilibrium is manifest and exposure to 1.5 ppm results in eye irritation without evidence of lung irritation.

Headache:

It would appear that exposure to PGDN vapor in concentrations as low as 0.1 ppm may have the potential for inducing headache in a susceptible segment of the population. Vapor exposure to the current TLV of 0.2 ppm resulted in the production of headache in the majority of individuals exposed for 4 or more hours. Repetitive exposure to this concentration resulted in the development of a tolerance characteristic to that described for workmen repetitively exposed to other nitrate compounds. This untoward response suggests that the current TLV may not afford the appropriate margin of safety.

The administration of 100% oxygen, black coffee, or aspirin generally ameliorated the head pain. Unfortunately, the study was too limited to permit

a ranking of these agents as to efficacy.

Neurological Abnormalities:

The marked impairment of the ability of the subjects exposed to 0.5 ppm for 6 to 8 hours to perform the heel-to-toe and modified Romberg test was very reminiscent of the response of the subjects tested in the same setting who were intoxicated with ethyl alcohol and who had blood alcohol concentrations in the 100 - 150 mg% range. Without question, this disturbance of equilibrium and sense of balance would represent a serious safety hazard.

Visual Evoked Response:

The consistent alteration in the VER observed in two groups of subjects tested 12 months apart indicates that exposure to PGDN in the concentrations studied can result in the disruption of the organization of the VER. The overall effect appears to be consistent with the VER changes produced by mild CNS depression. These data further suggest that the effects of exposure to the current TLV may be cumulative when the exposure is repeated at intervals of less than 24 hours. Exposure to the highest concentration studied, PGDN 1.5 ppm, resulted in an initial augmentation of the peak-to-peak amplitude of the 3-4-5 wave complex followed by a shift toward control levels. This shift may represent a successful accommodation to PGDN or it may represent the beginning of a more severe depression of the CNS.

Cardiovascular-Pulmonary Response:

No alteration occurred in the spirometric studies of those individuals who were complaining of eye irritation when exposed to 1.2 - 1.5 ppm. Of concern, however, was the consistent elevation of the diastolic pressure of those normotensive individuals exposed to 0.5 ppm for 8 hours. This narrowing of the pulse pressure as a result of diastolic pressure elevation has been observed in the grossly over-exposed to PGDN in the industrial setting. There was no indication of change in alteration of the basic cardiac rhythm or conduction times.

Other Untoward Subjective Responses:

Eye irritation was consistently present during exposure to PGDN 1.2 - 1.5 ppm. It was inconsistently present at lower concentrations and, hence, could not be used as a warning symptom of potential over-exposure.

During this series of studies the complaint of nasal stuffiness was uncommon.

Clinical Laboratory Studies:

The toxicity of PGDN in experimental animals has manifested anemia, pigment deposition in various tissues, fatty changes in the liver, methemoglobin formation, and greatly increased serum and urinary inorganic nitrates [9-11]. Over the range of concentrations studied in the healthy males, there was no biochemical or hematological evidence of a toxic effect upon a target organ.

ACKNOWLEDGEMENTS

The authors are grateful to H. C. Dodd, S. A. Graff, K. K. Donohoo, E. D. Baretta, and J. W. Mellender for their technical assistance in various phases of this study. The authors also gratefully acknowledge the constructive suggestions of R. C. Wands, Advisory Center on Toxicology, National Academy of Sciences - National Research Council; G. M. Lawton, M. D., Industrial Environmental Health Division, Bureau of Medicine and Surgery, Department of the Navy; and Dr. S. L. Friess, Physiological Sciences Department, Naval Medical Research Institute, National Naval Medical Center.

TABLE I

HUMAN EXPOSURE TO PGDN

Experiment	No. of Subjects	PGDN Concentration, ppm (Mean ± Standard Deviation)	Duration (hr.)
1 - 12	8	0.0	4.0
13	2	0.0	1.0
	6	0.0	4.2
14	2	0.1 ± 0.035	1.0
	3	0.1 ± 0.05	4.1
	3	0.1 ± 0.04	8.0
15	2	0.01 ± 0.01	1.0
	3	0.03 ± 0.01	4.0
	3	0.03 ± 0.01	8.0
16	2	1.20 ± 0.11	1.2
	6	1.46 ± 0.28	3.2
. . . . .			
17 - 27	9	0.0	4.0
28	3	0.0	1.0
	3	0.0	2.0
	3	0.0	3.0
29	3	0.47 ± 0.04	1.0
	3	0.51 ± 0.05	2.0
	3	0.50 ± 0.09	7.3
30	3	0.0	1.0
	3	0.0	2.0
	3	0.0	8.0
31	3	0.26 ± 0.04	1.0
	3	0.24 ± 0.03	2.0
	3	0.21 ± 0.04	8.0
32 - 35	9	0.0	4.0

Table I, continued

36	3	0.0	1.0
	3	0.0	2.0
	3	0.0	8.0
37	3	0.37 ± 0.05	1.0
	3	0.35 ± 0.04	2.0
	3	0.33 ± 0.04	8.0
38 - 39	9	0.0	4.0
40	3	0.24 ± 0.06	7.5
	3	0.24 ± 0.06	7.75
	3	0.24 ± 0.06	8.0
41	3	0.20 ± 0.04	7.5
	3	0.20 ± 0.04	7.75
	3	0.20 ± 0.04	8.0
42	3	0.30 ± 0.05	7.5
	3	0.30 ± 0.05	7.75
	3	0.30 ± 0.05	8.0
43	3	0.18 ± 0.04	7.5
	3	0.18 ± 0.04	7.75
	3	0.18 ± 0.04	8.0
44	3	0.22 ± 0.05	7.5
	3	0.22 ± 0.05	7.75
	3	0.22 ± 0.05	8.0

HUMAN EXPOSURE TO PGDN
PAIRED "t" VALUES FOR COMPARISON OF CONTROL vs EXPOSURE TEST SCORES

Test		CONCENTRATION, PPM					
		0.2		0.35		0.5	
Marquette Test		t	df	t	df	t	df
One Second Sound	E/S	0.666	8	0.092	5	-0.859	5
	|E-S|	-1.302	8	-0.071	5	1.507	5
	RxT	-0.634	8	-0.377	5	1.238	5
Three Second Sound	E/S	0.701	8	1.497	5	2.048	5
	|E-S|	-0.284	8	1.945	5	2.73	5
	RxT	-0.28	8	1.708	5	0.441	5
Five Second Sound	E/S	-0.37	8	1.925	5	1.200	5
	|E-S|	-1.677	8	0.797	5	1.834	5
	RxT	-0.036	8	0.296	5	0.723	5
One Second Light	E/S	0.443	8	0.122	5	0.801	5
	|E-S|	-0.279	8	-0.503	5	0.471	5
	RxT	-0.221	8	-1.360	5	0.644	5
Three Second Light	E/S	-1.294	8	-0.467	5	0.663	5
	|E-S|	-1.957	8	-1.654	5	-0.384	5
	RxT	-1.401	8	-0.483	5	-3.499*	5
Five Second Light	E/S	-0.985	8	-1.653	5	-0.000	5
	|E-S|	-2.254	8	2.925*	5	1.902	5
	RxT	-0.121	8	0.567	5	0.432	5
10 Second Estimation		0.351	8	1.154	5	2.077	5
30 Second Estimation		0.757	8	0.745	5	0.316	5
Arithmetic		-1.750	8	-1.908	5	-0.484	5
Coordination		0.407	8			0.462	7
Inspection		-3.311*	5	-6.425**	5	2.475	5
Collar & Pin		-3.658*	5	0.509	2	1.000	2

Significant at 95% level
nificant at 99% level

E = Estimate
S = Stimulus Duratic
Rxt = Reaction Time

FIGURE 1

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

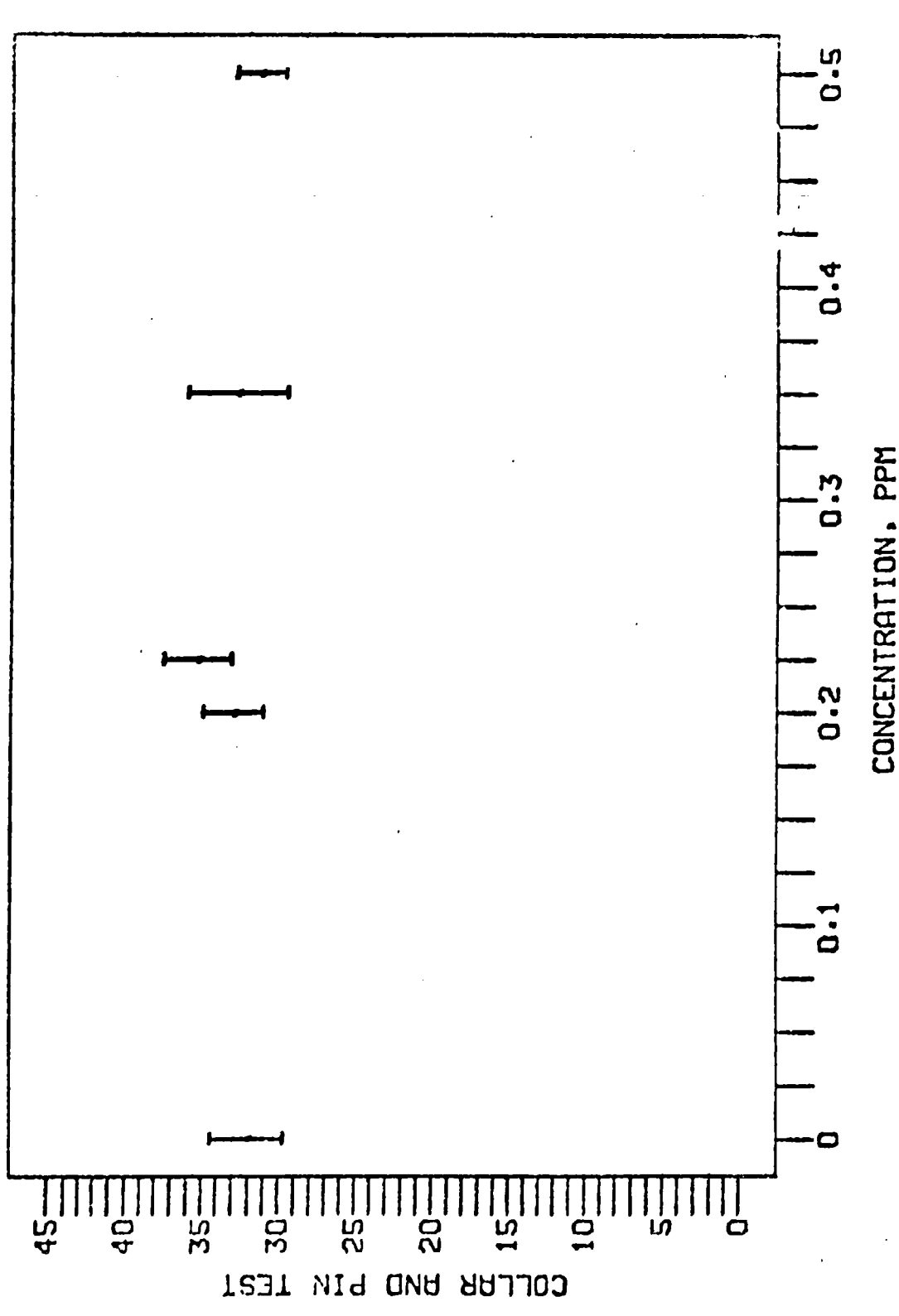


FIGURE 2

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

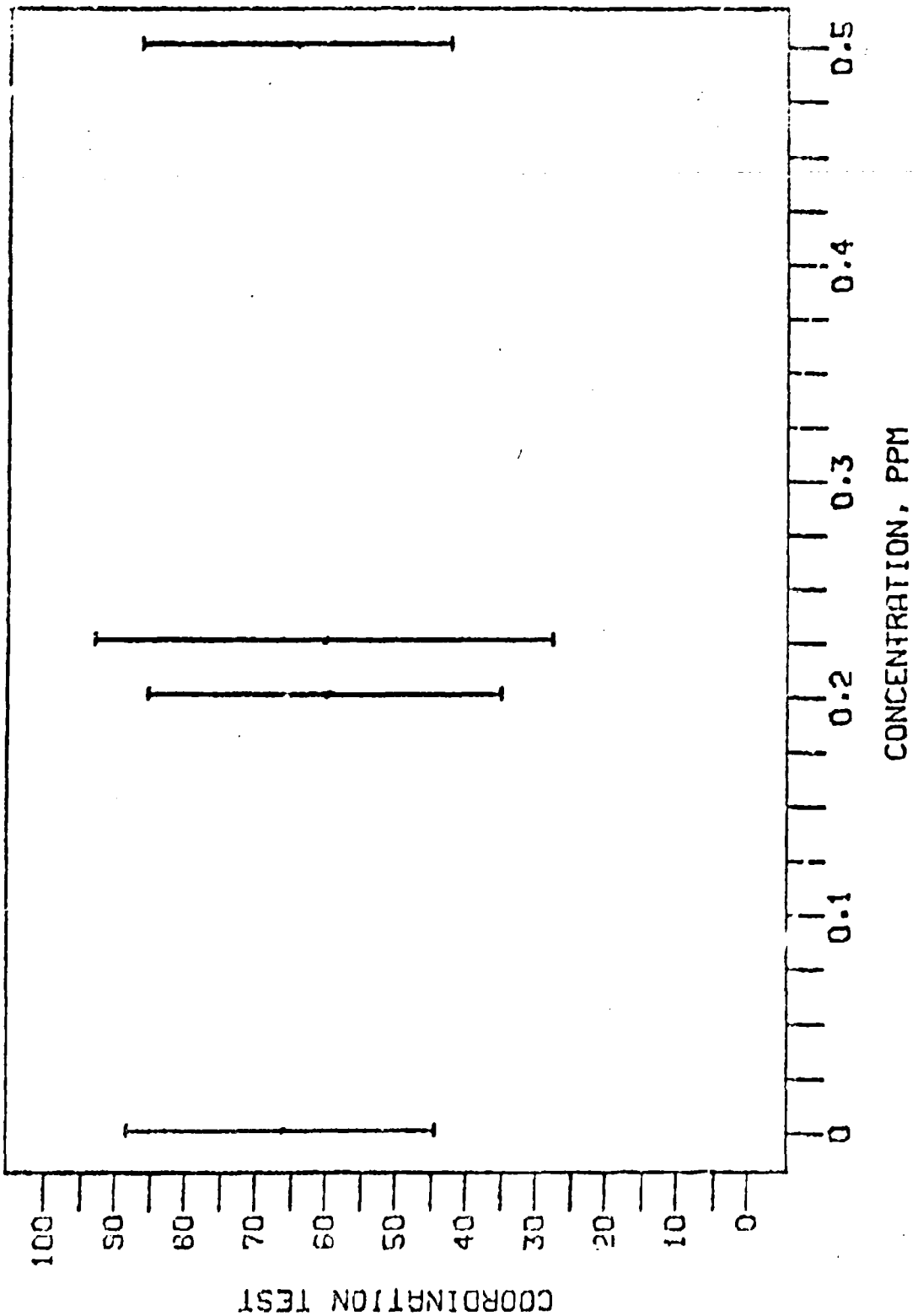


FIGURE 3

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

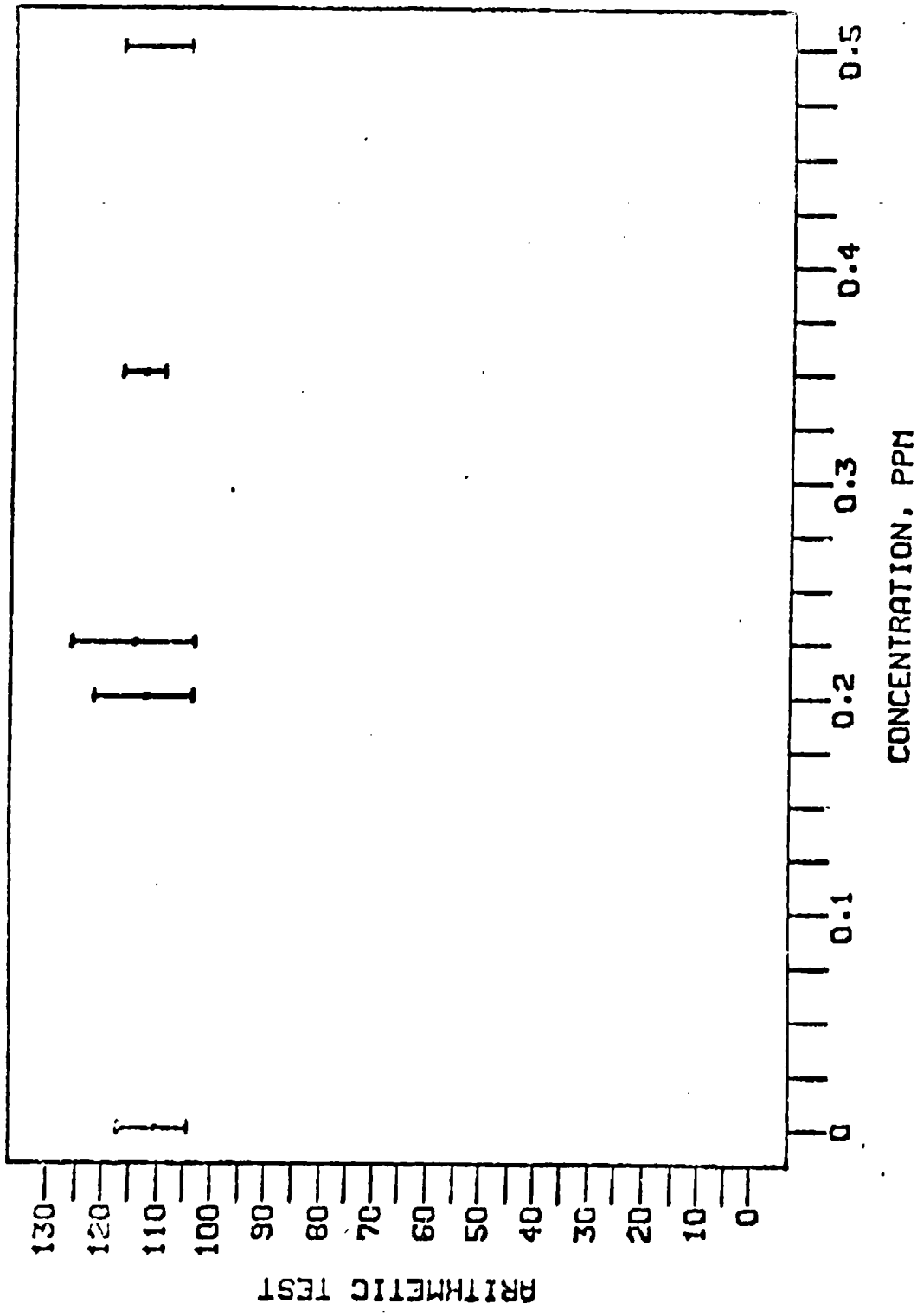


FIGURE 4

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

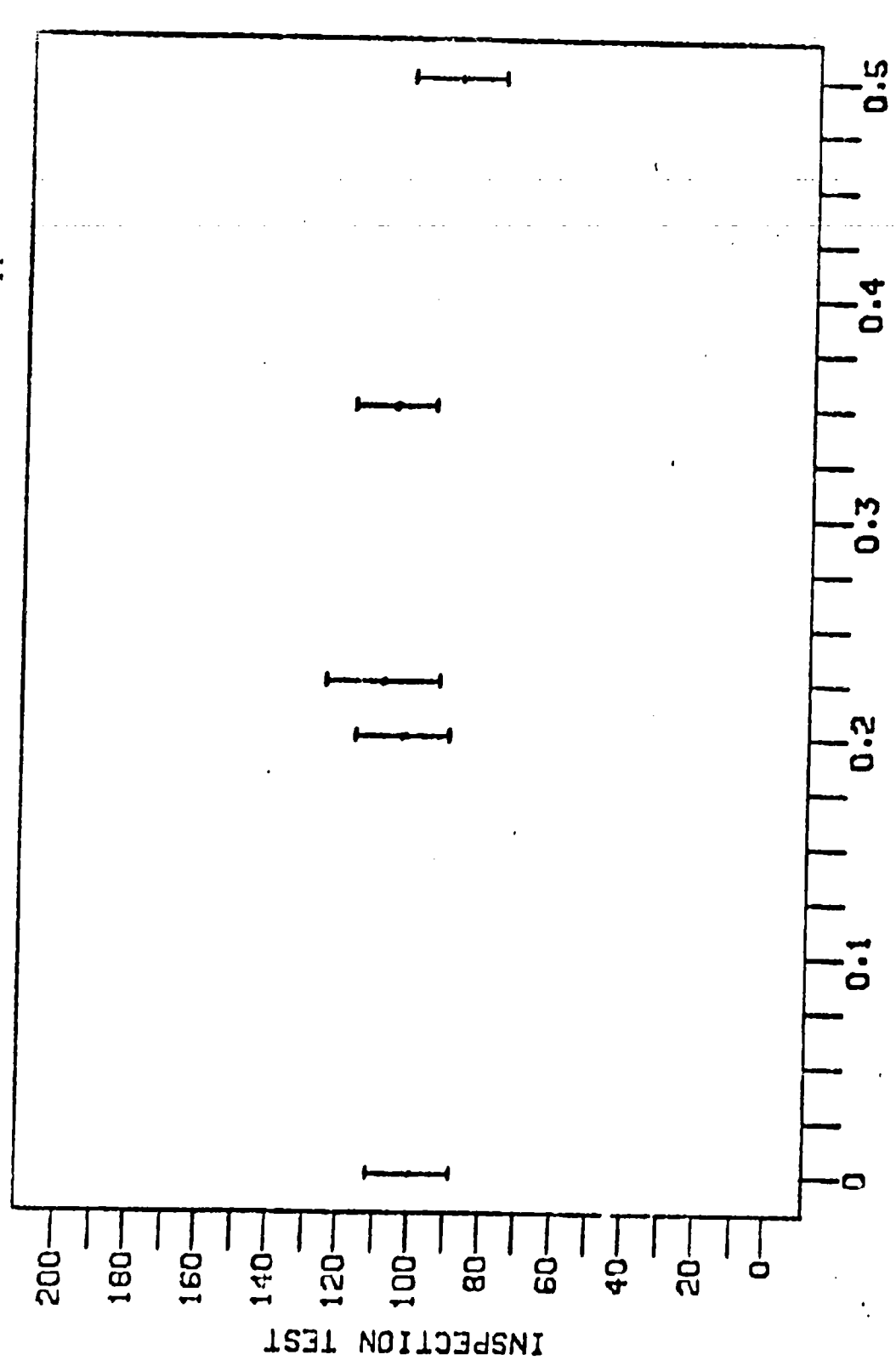


FIGURE 5

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

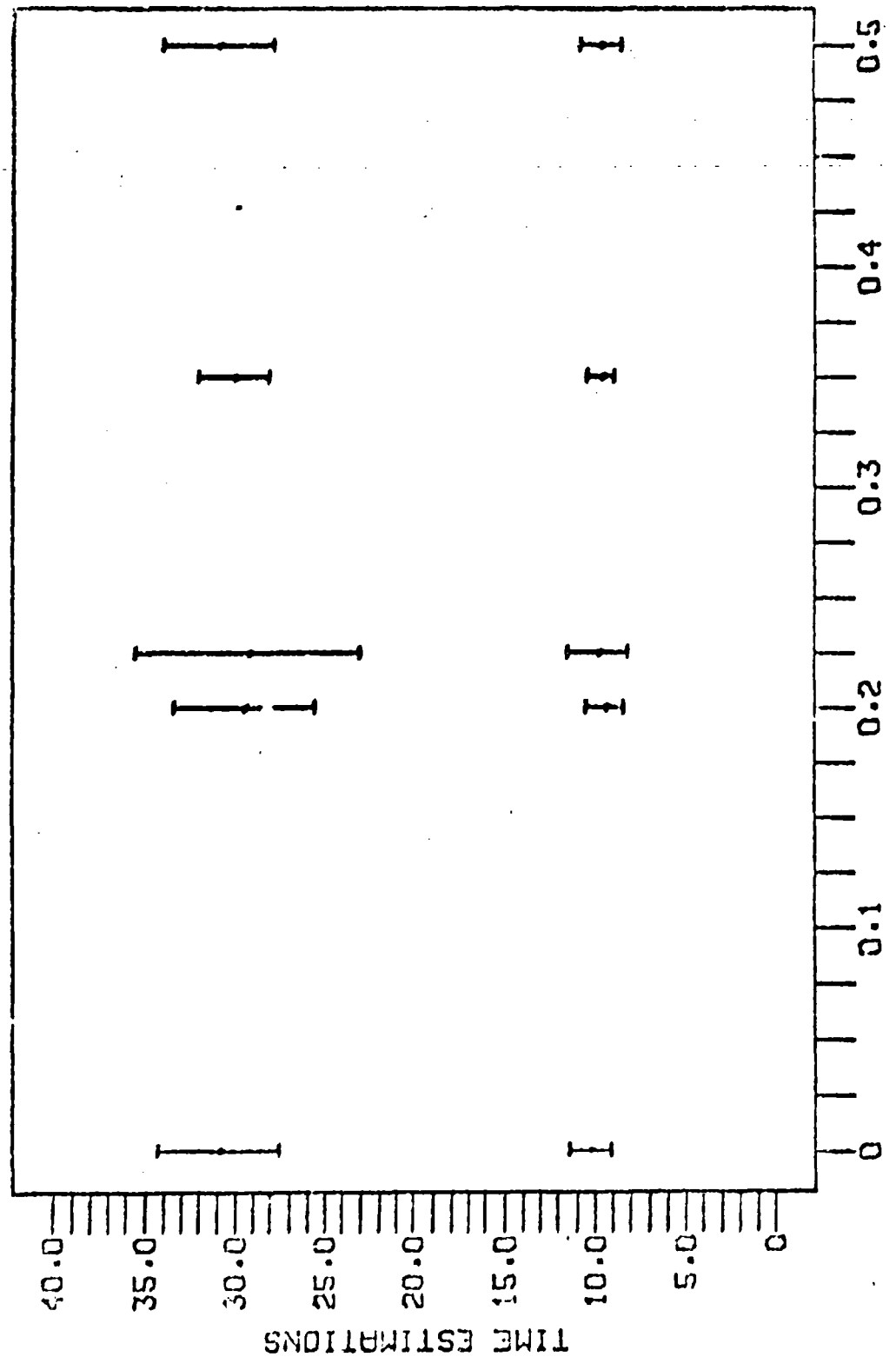


FIGURE 6

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

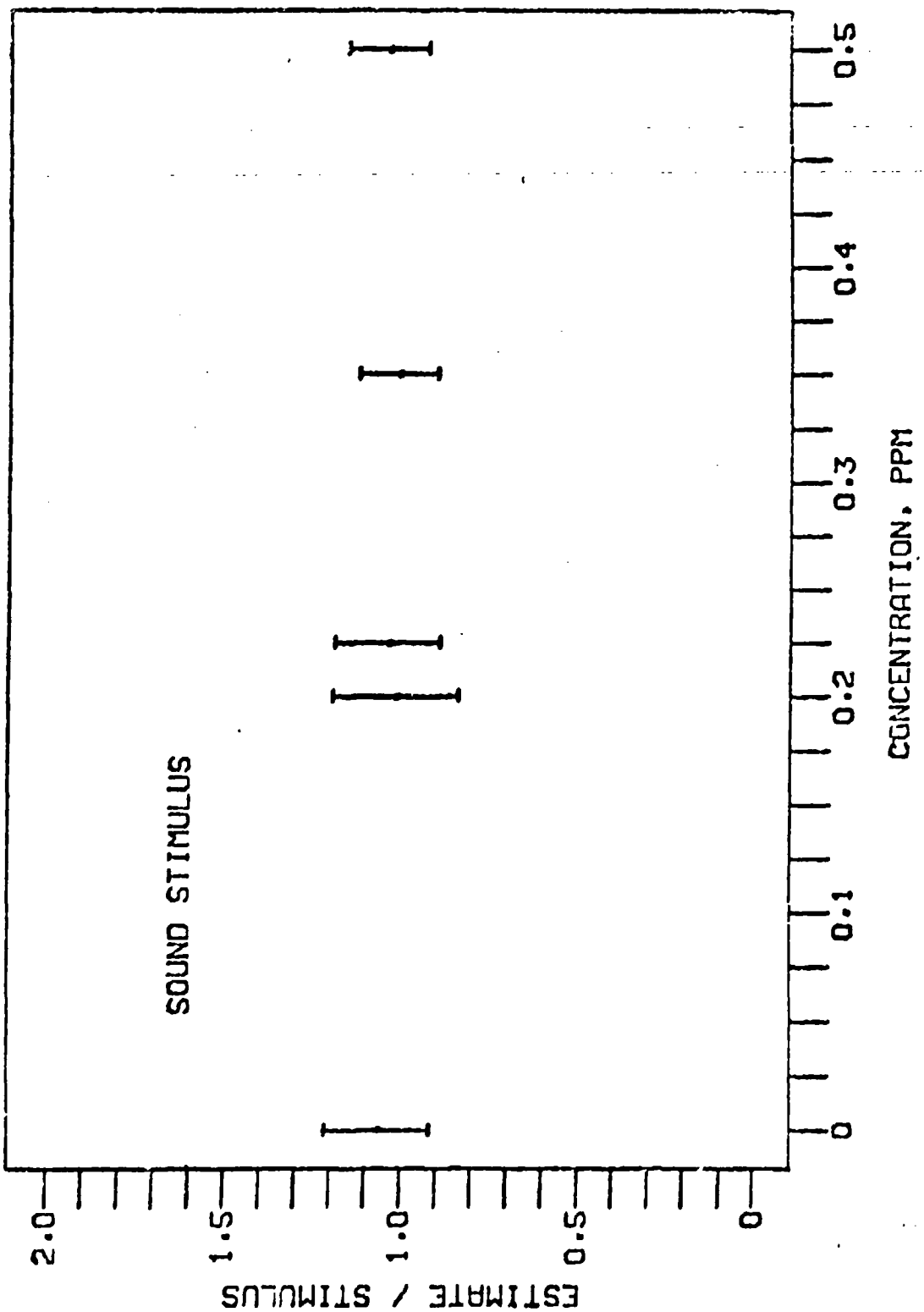


FIGURE 7

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

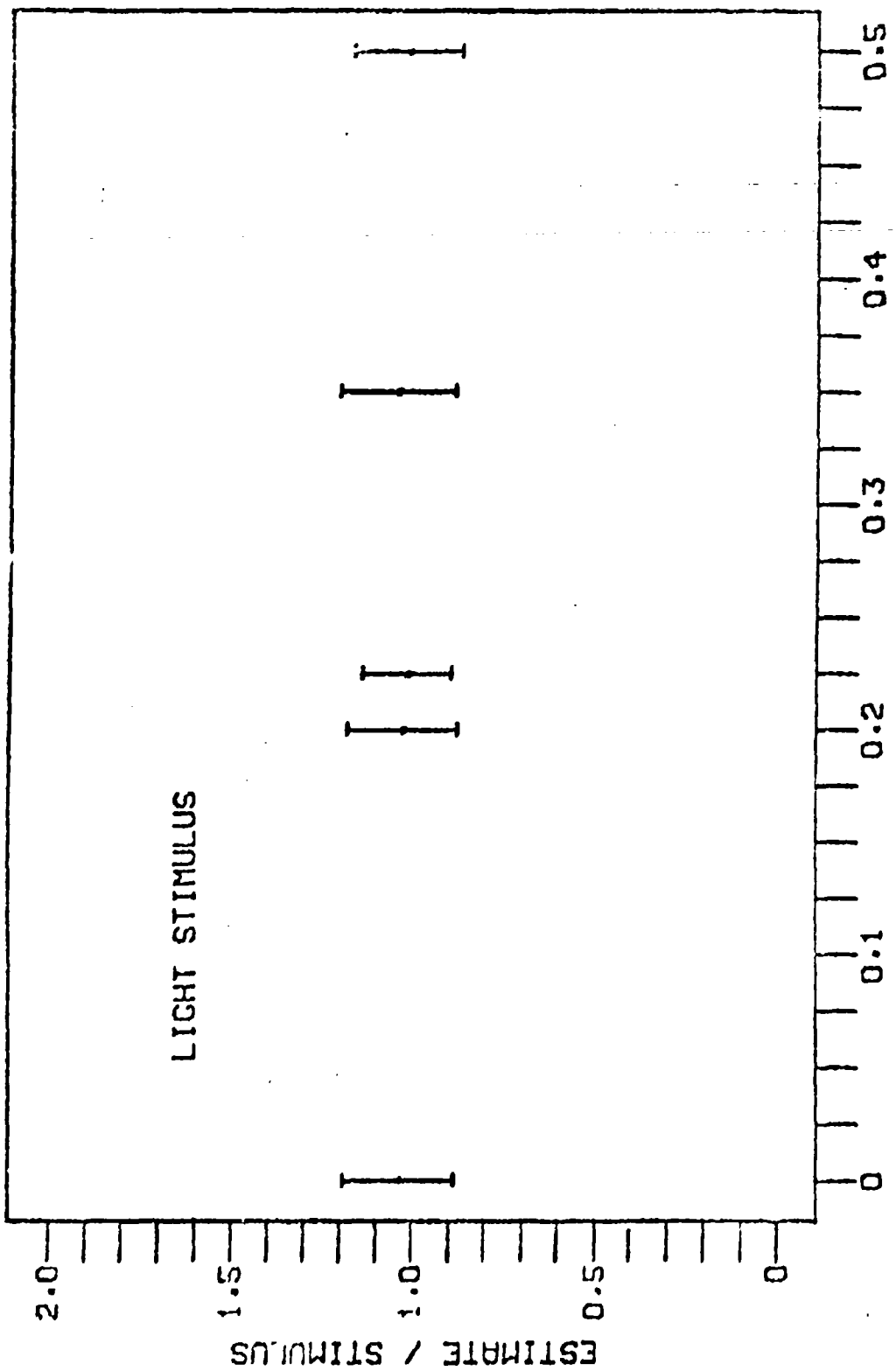


FIGURE 8

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

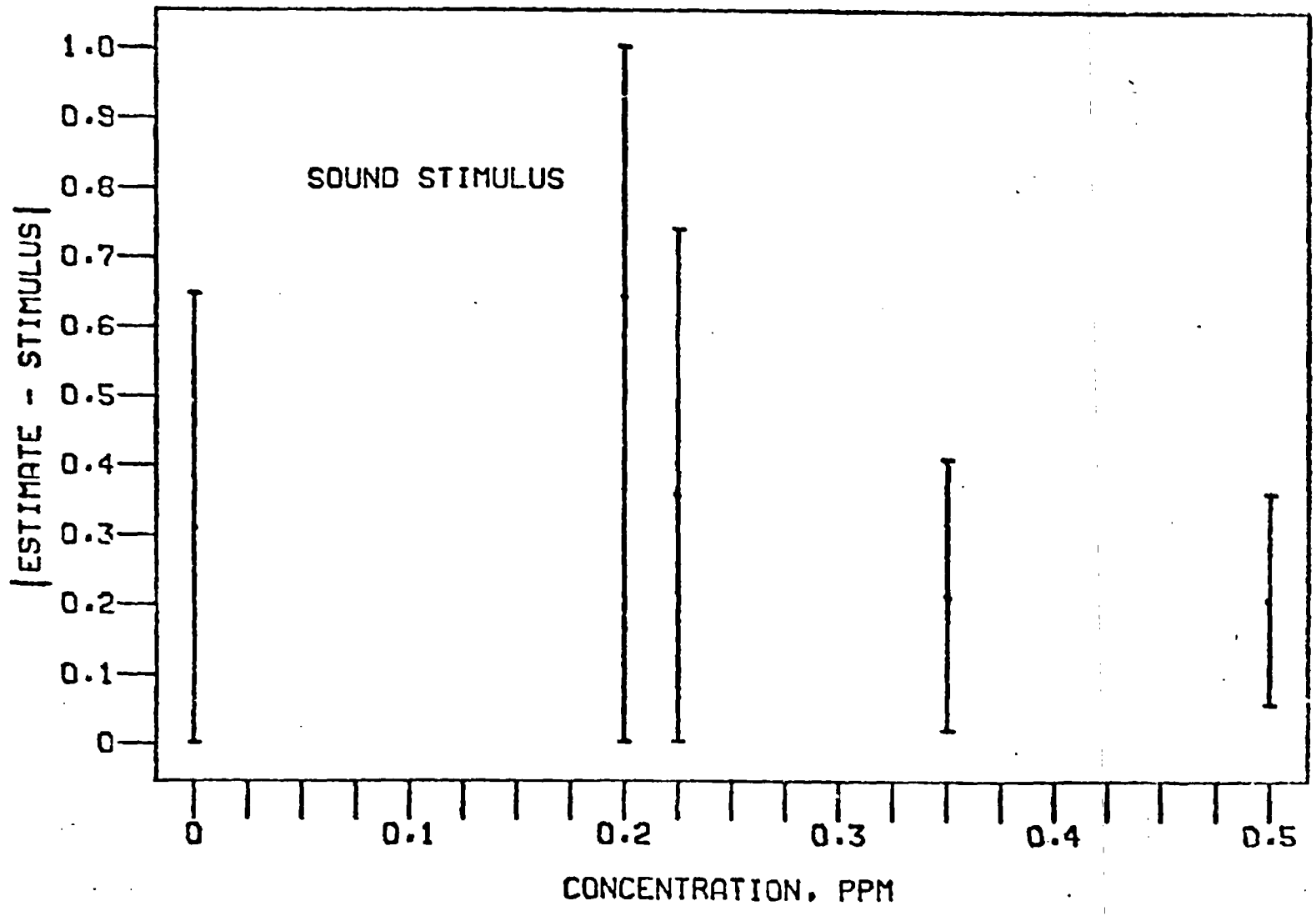


FIGURE 9

HUMAN EXPOSURE TO FCDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

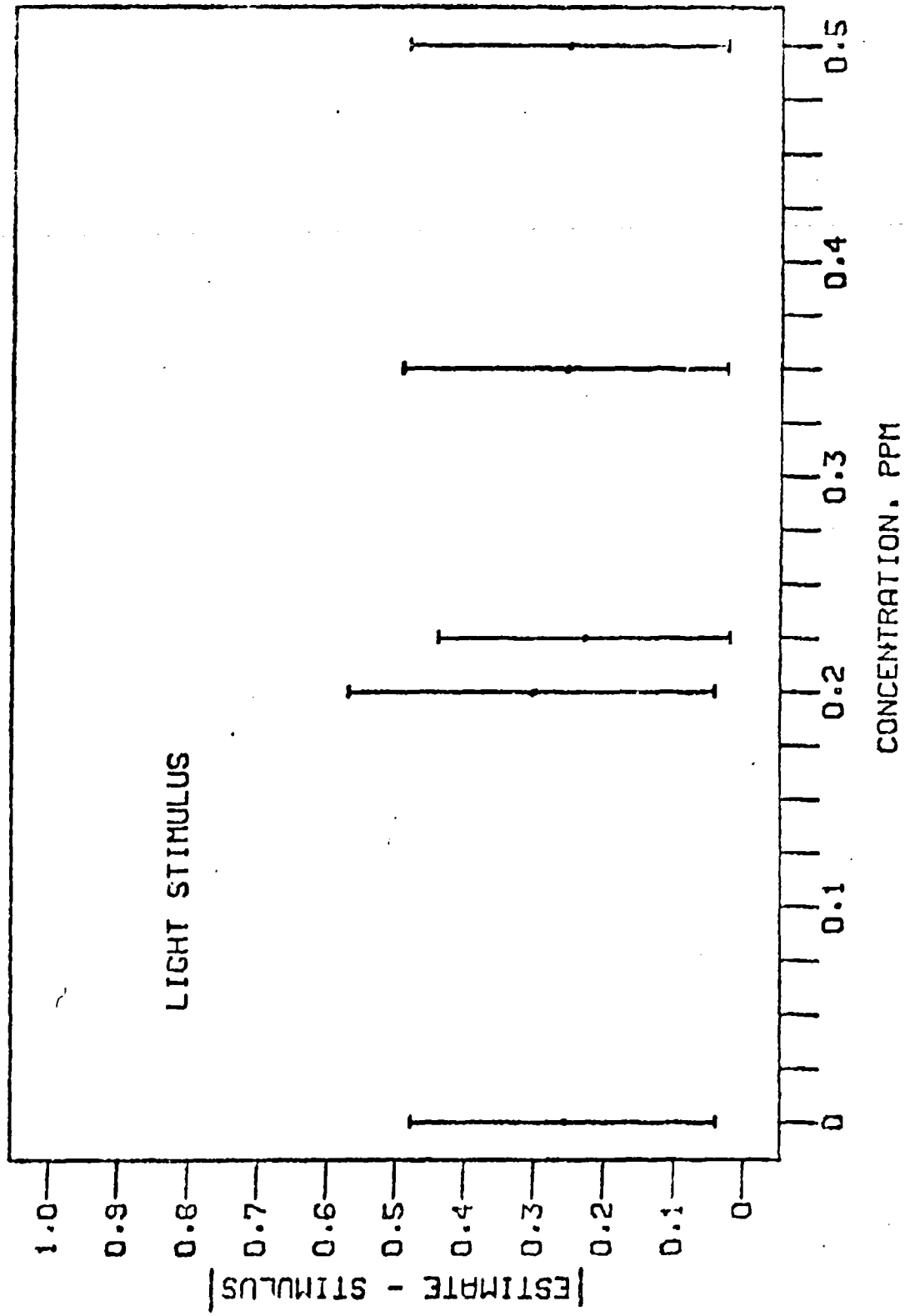


FIGURE 10

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

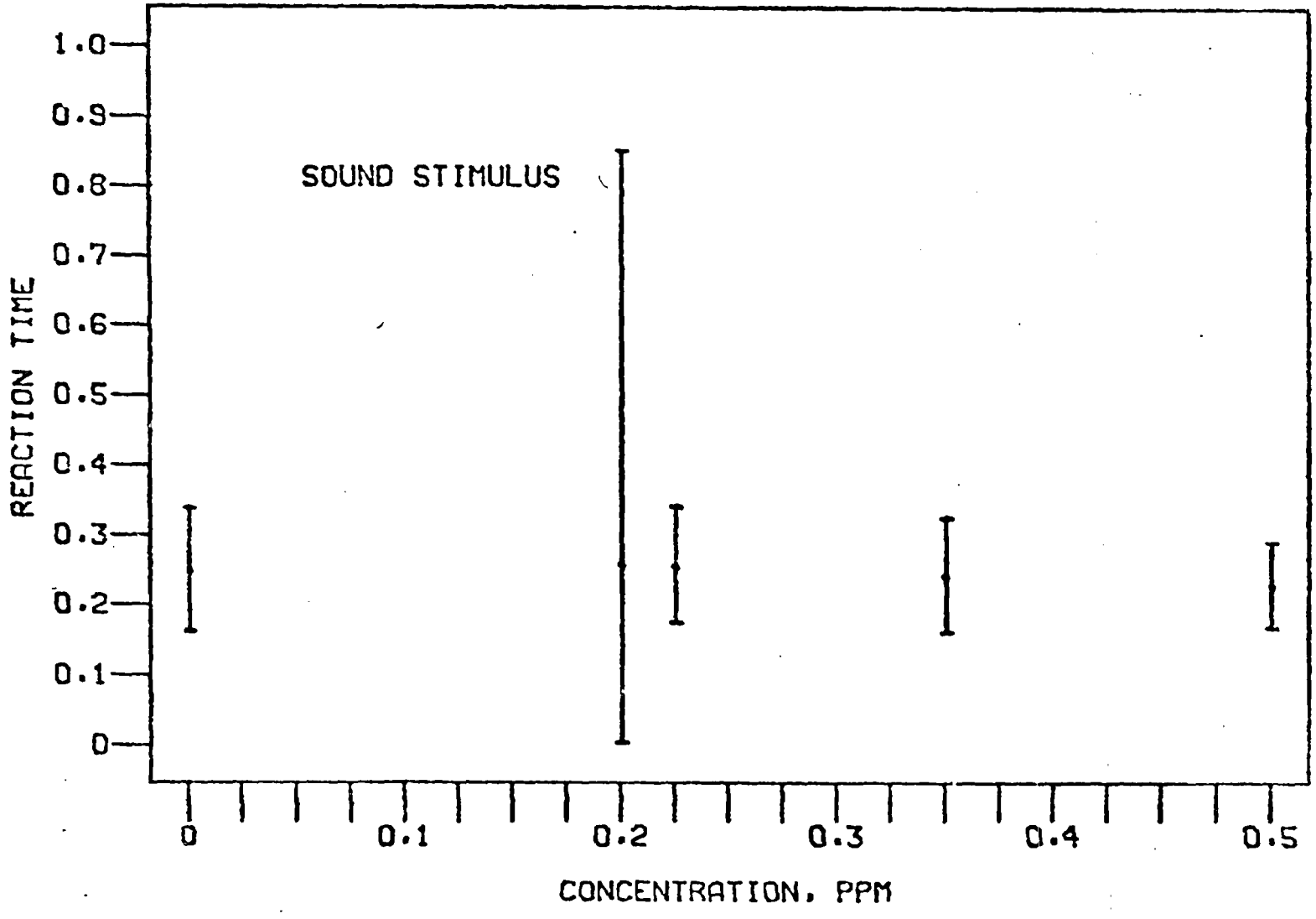


FIGURE 11

HUMAN EXPOSURE TO PGDN

Mean score and range are plotted. The score plotted at 0.225 ppm was the score achieved on the fifth day of exposure to 0.2 ppm.

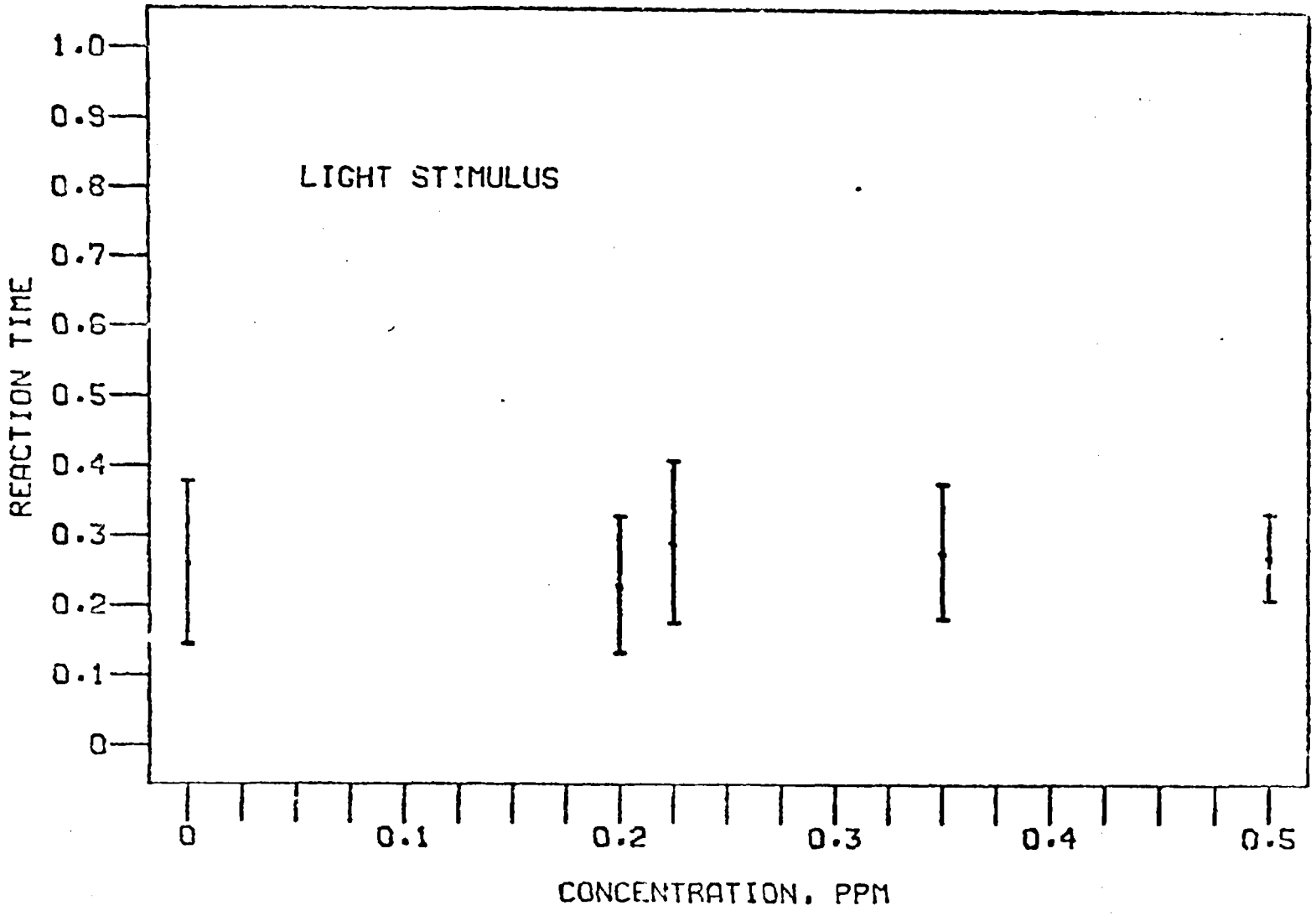
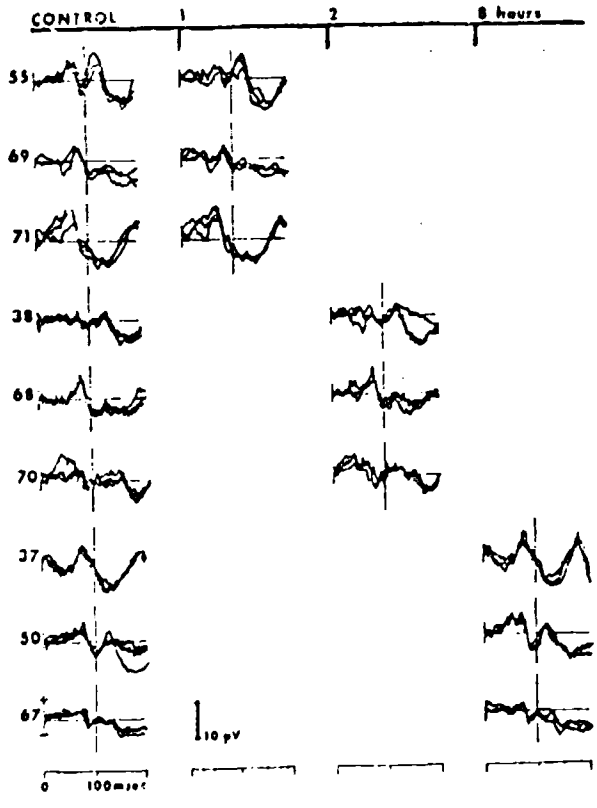


Figure 12

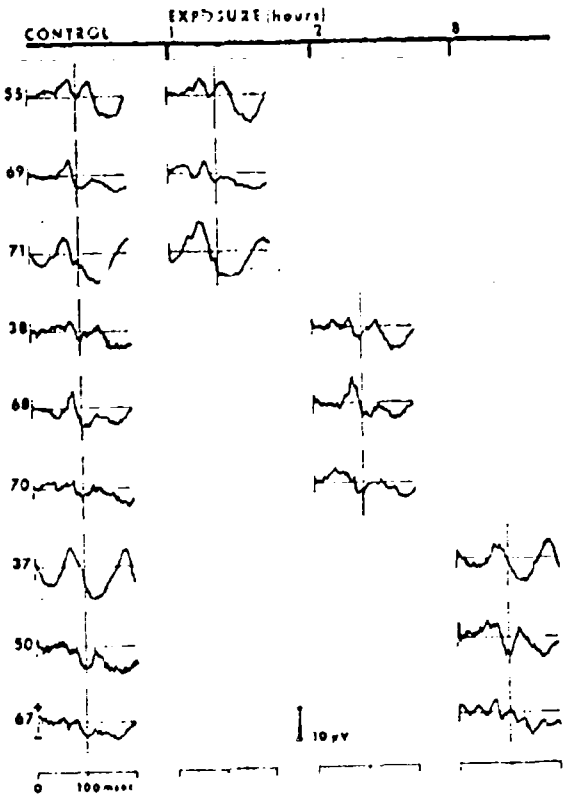
HUMAN EXPOSURE TO PGDN



VER responses from three control exposures are superimposed. Each potential represents the average of 100 responses. Flash rate, 1 Hz. Polarity and voltage as indicated.

Figure 13

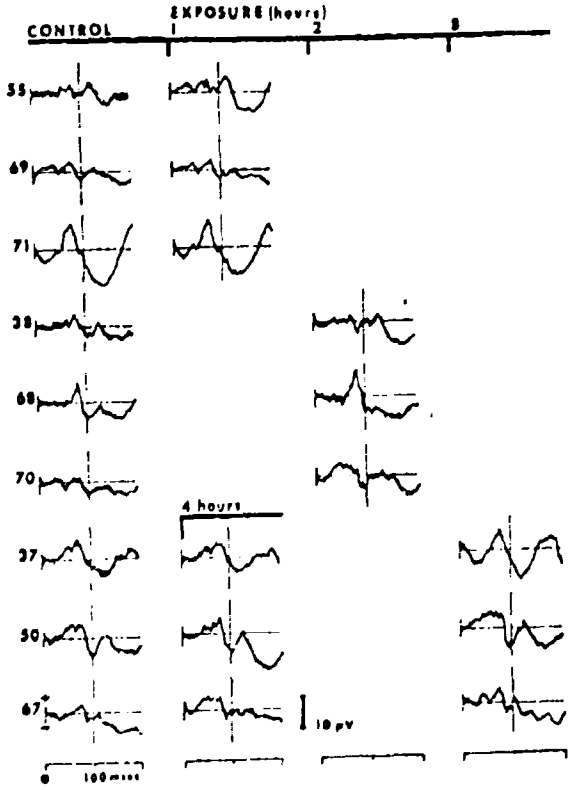
HUMAN EXPOSURE TO PGDN 0.2 PPM



Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity and voltage as indicated.

Figure 14

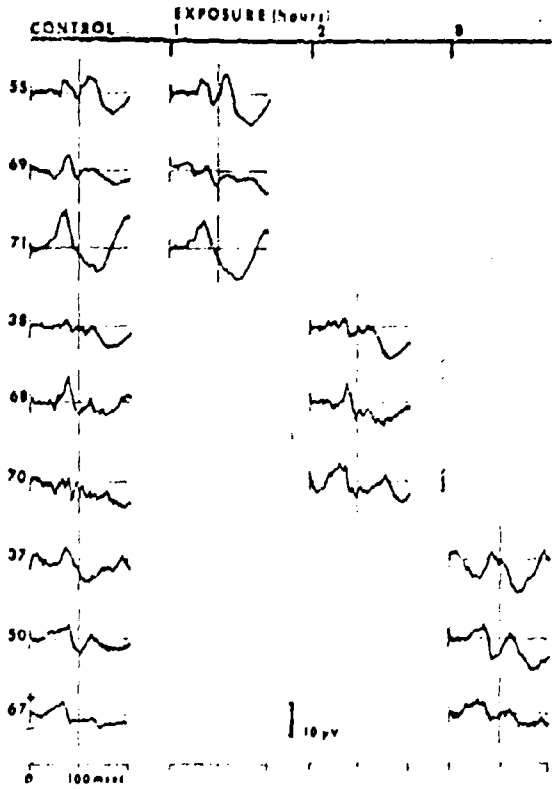
HUMAN EXPOSURE TO PGDN 0.35 PPM



Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity and voltage as indicated.

Figure 15

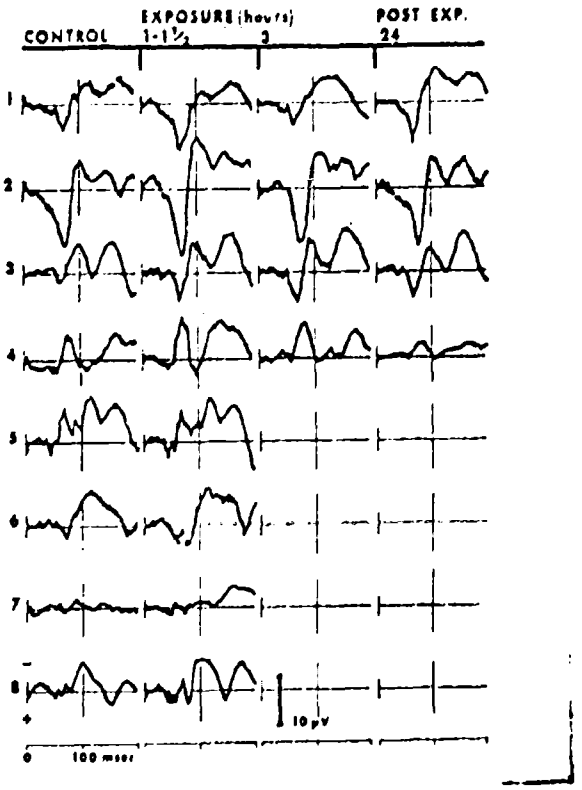
HUMAN EXPOSURE TO PGDN 0.5 PPM



Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity and voltage as indicated.

Figure 16

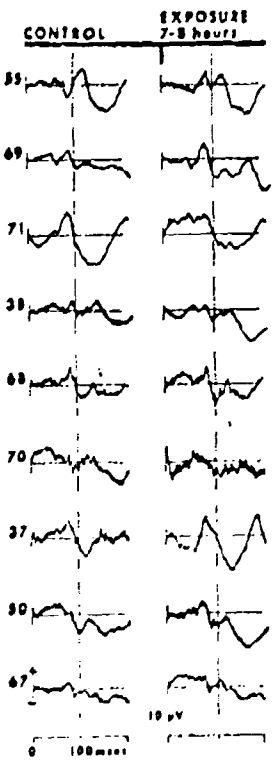
HUMAN EXPOSURE TO PGDN 1.5 PPM



Each VER represents the average of 100 responses. Flash rate, 0.5 Hz. Polarity and voltage as indicated.

Figure 17

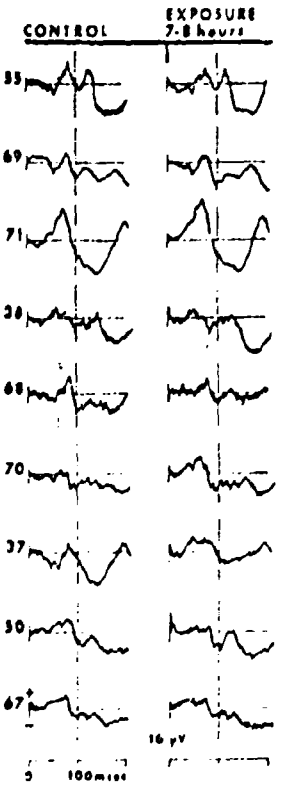
HUMAN EXPOSURE TO PGDN 0.2 PPM



Day 1 of 5-day exposure sequence. Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity as indicated. Calibration voltage same as Figure 15.

Figure 18

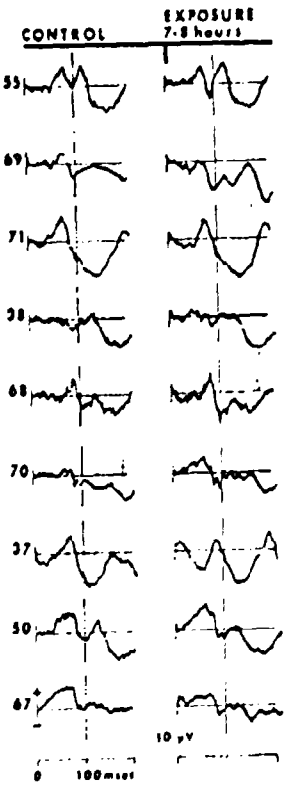
HUMAN EXPOSURE TO PGDN 0.2 PPM



Day 2 of 5-day exposure sequence. Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity as indicated. Calibration voltage same as Figure 15.

Figure 19

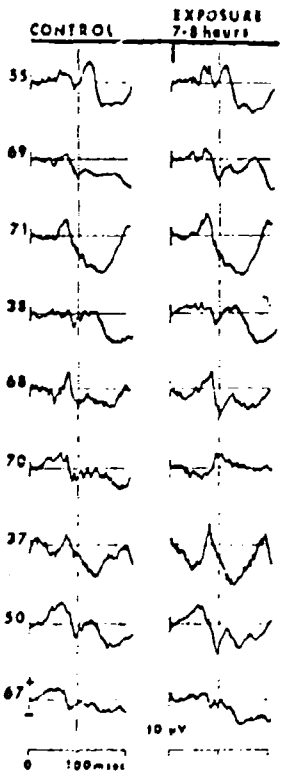
HUMAN EXPOSURE TO PGDN 0.3 PPM



Day 3 of 5-day exposure sequence. Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity as indicated. Calibration voltage same as Figure 15.

Figure 20

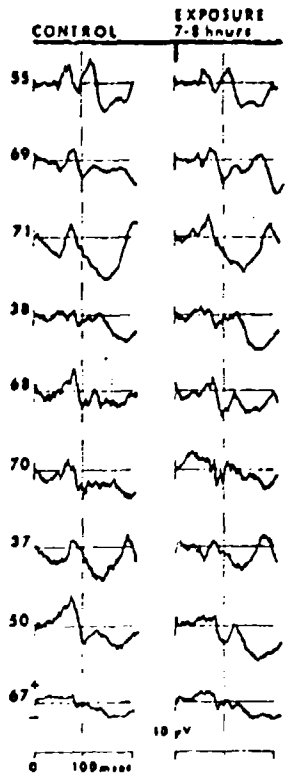
HUMAN EXPOSURE TO PGDN 0.2 PPM



Day 4 of 5-day exposure sequence. Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity as indicated. Calibration voltage same as Figure 15.

Figure 21

HUMAN EXPOSURE TO PGDN 0.2 PPM



Final day of 5-day exposure sequence. Each VER represents the average of 100 responses. Flash rate, 1 Hz. Polarity as indicated. Calibration voltage same as Figure 15.

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